



The role of water in the reusability of aminated silica catalysts for aldol reactions

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ABSTRACT

The reusability of methylaminopropyl active sites grafted on mesoporous amorphous silica, either with cooperative silanol groups or trimethylsilylated, was assessed in the aldol reaction of acetone with 4-nitrobenzaldehyde. Raman, ¹³C NMR, and UV–Vis spectroscopy demonstrated the presence of stable enamines on the spent catalysts. These enamines are produced as a side product from iminium intermediates in the catalytic cycle. Water co-feeding enhances the desorption of the iminium intermediates and, hence, suppresses the formation of these stable enamine species. The reusability of the cooperative catalyst increased to 70% with co-feeding 0.69 wt% water, while an almost complete reusability was achieved for the trimethylsilylated catalyst. Continuous-flow experimentation showed that the cooperative effect of the silanol groups was lost during the first 7 h on-stream, yet activity losses continued, most likely due to silica hydrolysis. Activity losses persisted on the more hydrophobic trimethylsilylated catalyst, but were significantly less pronounced.

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1. Introduction

Aldol reactions constitute an important class of reactions to produce new carbon-carbon bonds in a wide range of processes, such as in the production of chalcones in the pharmaceutical industry [1] and 2-ethylhexanol for PVC plasticizers [2]. A potential novel application in the bio-based industry is the production of liquid fuels from lignocellulosic biomass by upgrading smaller furanic molecules, such as 2-furaldehyde (furfural) and 5-(hydroxymethyl) furfural (HMF), to heavier hydrocarbons [3]. At present, commercial scale aldol reactions are catalyzed by a homogeneous, strong base catalyst, such as NaOH, which permits to perform the reaction even at room temperature [4]. However, these catalysts also exhibit several important disadvantages, such as a short lifetime, an environmental risk, equipment corrosion and an energy intensive separation from the reaction products [5,6]. Hence, the pursuit of a reusable, heterogeneous catalyst could lead to a more sustainable

alternative production route. In this sense, either an acidic or a basic heterogeneous catalyst can be employed.

Heterogeneous acid catalysts, such as the widely employed zeolite-type materials, have already been investigated for liquid-phase aldol reactions [7–9]. However, unlike base catalysts, the Brønsted acid function in zeolites promotes undesired side reactions such as isomerization and cyclodehydration [9]. Moreover, the formation of large condensation products inside the micropores causes rapid pore-blocking and subsequent deactivation [10]. Development of zeolites with larger mesopores reduces the catalyst's susceptibility to coking, but also decreases its acid strength [8]. Hence, acidic zeolite-type materials appear not ideal as reusable, sustainable heterogeneous catalysts for liquid-phase aldol reactions.

Candidate heterogeneous base catalysts for liquid-phase aldol reactions comprise mixed oxide materials such as hydrotalcite based catalysts [11–17], ion-exchange resins [18], and cooperative acid-base silica catalysts [19–37]. The mixed oxide and hydrotalcite materials typically suffer from fast deactivation by strong adsorption of reagents and ambient CO₂ during storage. Complete

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regeneration of its basic character is difficult [14,15]. Additionally, side-reactions such as the Cannizzaro reaction, typically occur to a significant extent on such catalysts [38]. Anion-exchange resins are composed of quaternary ammonium ions interacting with free OH^- ions, which are the actual active sites. These catalysts are also subject to deactivation, caused by neutralization of the OH^- ions and pore-blocking [39,40]. Aminated mesoporous silica materials, either ordered or amorphous, possess large mesopores and have basic amine sites [41]. Despite a typically lower activity, these materials are less prone to pore-blocking by large condensed products.

The idea for using amines in aldol reaction reactions originates from natural aldolase enzymes, which catalyze aldol reactions via an enamine-type mechanism [42]. List et al. [43] employed the amino acid L-proline as a homogeneous catalyst in the aldol reaction of 4-nitrobenzaldehyde with acetone in dimethylsulfoxide (DMSO). They proposed a cooperative effect between the acidic carboxylate and the basic amine: the acid function promotes the nucleophilic attack of the basic amine on this carbonyl group, and assists in proton-transfers [43]. A heterogeneous amine catalyst can be synthesized by functionalizing aminosilanes on silica [19–35,44]. The weakly acidic silanol groups, which are intrinsically present at the silica surface, act as the cooperative partner in the reaction mechanism, equivalent to the cooperative effect of the carboxyl group in L-proline [28,37]. Secondary amines are preferred, since primary amines allow the formation of a stable inhibiting imine species, and tertiary amines do not allow the formation of the crucial enamine intermediate [22,23]. However, care should be taken that the substituent on the secondary amine is not too large, in order to minimize steric hindrance when approaching the nitrogen lone electron pair [24]. It has been shown that a methyl substituted secondary amine with a propane linker on a mesoporous amorphous silica is an efficient catalyst for the aldol reaction when silanol groups are neighboring the amine [25–27]. Previously it was found that, when the amines are grafted randomly on the surface, at least 1.7 of these silanol groups are required per amine function to assure full promotion [29]. Increasing the acid strength of the promoting acid function has been observed to decrease the catalytic activity [30–33]. This can be explained by an unfavorable shift in the equilibrium of the free acid base couple to the neutralized one [30]. Hence, currently the most active aminated mesoporous amorphous silica catalyst for aldol reactions is a secondary amine, with a small substituent such as a methyl group, promoted by an excess of silanol groups.

Not only the activity, but also the catalyst stability is an important factor to take into account when assessing the commercial potential of a catalyst [45]. This means that a catalyst should exhibit the same level of activity throughout its lifetime. However, due to the nature of a batch reactor, deactivation cannot be observed separately from the normal time-evolution in the course of a single experiment. Hence, recycling of the spent catalyst in a subsequent experiment should be performed. Opposed to a batch-type reactor, a continuous-flow reactor can be used to observe catalyst deactivation directly by measuring the catalytic activity with time-on-stream. This allows for more detailed insights into the specific deactivation behavior and corresponding mechanism. For aldol reactions using homogeneous L-proline, Zovota et al. [46] identified off-cycle species such as oxazolidinones and oxapyrrolizidines, using H-NMR, when insufficient water is present. We have also recently reported that an ethylene-bridged ordered periodic mesoporous organosilica material, functionalized with cysteine, exhibits a lower turnover frequency (TOF) in a recycle experiment [35]. Shylesh et al. [23] have performed gas-phase self-aldol reaction of butanal in a continuous-flow reactor on a cooperative acid-base mesoporous amorphous silica catalyst, but reported no information about catalyst deactivation with time-on-stream. Clearly

no detailed information about the deactivation behavior of aminated silica materials has been reported yet for aldol reactions.

In the present work, our aim is to systematically investigate the phenomena potentially involved in catalyst deactivation in heterogeneous amine catalyzed aldol reactions. Consecutive experiments in a batch-type reactor have been performed as well as time-on-stream experiments in a continuous-flow reactor. Using a variety of characterization techniques combined with mechanistic insights, conditions have been identified whereby the recyclability of the aminated mesoporous amorphous silica catalysts for the aldol reaction approaches 100%.

2. Experimental procedures

2.1. Synthesis of the cooperative acid-base catalyst and the monofunctional base catalyst

The procedure for grafting secondary amine functional groups on mesoporous amorphous silica, and the endcapping of the silanol groups with trimethylsilyl groups, was reported more elaborately before [24] and is briefly summarized here. Silica gel 60 (grade 7734, Sigma-Aldrich) was used as a catalyst support material. For experiments in the batch reactor, a pellet size range between 63 μm and 210 μm was employed. For the continuous-flow reactor, the pellet size was increased to a range between 250 μm and 500 μm to avoid a significant pressure drop over the catalyst bed. The support material was first heated at a rate of 2 $^{\circ}\text{C}/\text{min}$ and calcined in air at 700 $^{\circ}\text{C}$ for 6 h. After calcination, the material was maintained at a temperature of 150 $^{\circ}\text{C}$ to avoid adsorption of moisture. Next, 5 g of the hot support material was suspended in 30 mL of toluene (Sigma-Aldrich, anhydrous, 99.8%). The amine precursor, N-methylaminopropyltrimethoxysilane (MAPTMS, ABCR), was subsequently added with a molar ratio of precursor to free silanol groups of 0.25. The necessary volume of precursor is calculated assuming that, because of the employed calcination procedure, the number of free silanol groups is equal to 1.1 OH/nm^2 [21]. To ensure full promotion of each randomly grafted amine site by the silanol groups, at least 1.7 silanol groups are required per amine site [29]. Hence, in this work a ratio of 4 free silanol groups for each methylaminopropyl function was employed. After adding the precursor, the mixture was refluxed for 24 h at 110 $^{\circ}\text{C}$ under an argon atmosphere. The obtained catalyst was then filtered and subsequently stirred in 250 mL chloroform (>99.8%, <50 ppm H_2O , Carl Roth) for 4 h. After vacuum drying for 24 h at room temperature, the cooperative acid–base catalyst was ready to be used in catalytic experiments. A desiccator was used for storage of the catalysts in order to avoid modifications due to the presence of atmospheric water vapor.

To obtain the monofunctional base catalyst, the silanol groups of the cooperative material were endcapped with trimethylsilyl groups [29,47]. For this, 5 g of the dried cooperative acid-base catalyst was completely covered with 100 mL of 1,1,1,3,3,3-hexamethyldisilazane (99%, HMDS, ABCR). The mixture was then stirred at room temperature for 4 h, subsequently filtered, and stirred in 250 mL chloroform (>99.8%, <50 ppm H_2O , Roth) for 4 h. After vacuum drying for 24 h at room temperature, the monofunctional base catalyst was ready to be used in catalytic experiments. This catalyst was also stored in a desiccator.

2.2. Characterization of the fresh and spent catalysts

Nitrogen adsorption-desorption measurements were carried out at $-196\text{ }^{\circ}\text{C}$, using a Micromeritics Tristar II surface area and porosity analyzer. The specific surface area and pore volume were determined using the Brunauer–Emmett–Teller (BET) method. The

average pore size and pore volume was obtained using the Barrett–Joyner–Halenda (BJH) method.

The concentration of amine groups was determined via elemental (CHNS) analysis. These measurements were performed on a Thermo Flash 2000 elemental analyzer using V_2O_5 as catalyst, in order to ensure the total oxidation of the sample. The mass percent of nitrogen in the sample is obtained by referring the obtained peak area to a calibration curve of methionine (USP, 99%) that was obtained prior to the measurements. Conversion to the concentration of active sites, in mol per gram, was then performed with the molar mass of nitrogen.

The presence of organic species on the catalyst surface, both before and after reaction, was determined with Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, as well as Raman spectroscopy. The DRIFT spectra were recorded using a Nicolet 6700 by Thermo Scientific with a liquid nitrogen cooled MCT-A detector, using a Graseby Specac diffuse reactant cell, operating in vacuum at 140 °C. The Raman spectroscopy was performed on a NXR FT-Raman module of Thermo Scientific, with a laser of 1064 nm and an InGaAs detector. A resolution of 4 cm^{-1} was used on a total of 512 scans per sample at a laser intensity of 0.31 W.

The ^{13}C CP/MAS NMR spectra were recorded at 100.61 MHz on a Bruker Avance III HD 400 WB NMR spectrometer at room temperature. An overall of 1000 free induction decays were accumulated. The excitation pulse and recycle time were 6 ms and 2 s. Chemical shifts were measured relative to tetramethylsilane standard. All samples were dried at 120 °C for 24 h prior to analysis.

UV–Vis diffuse reflection measurements were performed using a Varian Cary 500 UV–Vis–NIR spectrophotometer equipped with an internal BaSO_4 -coated integrating sphere.

2.3. Determination of the water content in stock organic solvents

To quantify the amount of water in the organic solvent dimethylsulfoxide (DMSO, $\geq 99\%$, FG, Sigma-Aldrich) and acetone (99.6%, Acros), Karl-Fischer titrations were performed on a MKC-501 coulometric cell with diaphragm (Kyoto Electronics). For DMSO, anolyte solution Hydranal Coulomat AG (Sigma-Aldrich) and catholyte solution Hydranal Coulomat CG (Sigma-Aldrich) were used. For acetone, methanol-free anolyte solution Hydranal Coulomat AK (Sigma-Aldrich) and methanol-free catholyte solution Hydranal Coulomat CG-K (Sigma-Aldrich) were used.

Karl-Fischer titrations indicated an average water content in stock acetone of $0.31 \pm 0.05\text{ wt}\%$ and in DMSO of $0.09 \pm 0.03\text{ wt}\%$. Both acetone and DMSO were stored under an argon atmosphere in order to minimize any absorption of ambient water. It was confirmed that storage under these circumstances during the course of the experimentation did not significantly change the amount of water in both DMSO as well as in acetone.

2.4. Drying of stock acetone

In order to further decrease the amount of water in the reactor, some experiments were performed with dried acetone. To remove water, 100 mL acetone was poured on 10 g freshly regenerated 3 Å molecular sieves (Sigma-Aldrich) and thoroughly mixed for one hour. This resulted in a 3-fold decrease in the water content to $0.09 \pm 0.02\text{ wt}\%$.

2.5. Catalytic performance evaluation of the fresh and spent catalysts in the batch reactor

The catalyst performance was initially evaluated in a batch-type reactor (Parr 4560 mini, 300 mL). The detailed procedure has been reported previously [24] and is also briefly summarized here. The considered benchmark reaction is the aldol reaction of acetone

(99.6%, Acros) with 4-nitrobenzaldehyde (99%, Acros), resulting in 4-hydroxy-4-(4-nitrophenyl)butan-2-one as aldol adduct and 4-(4-nitrophenyl)-3-buten-2-one as condensate, see Scheme 1.

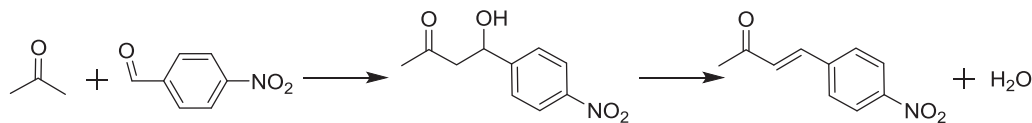
To start an experiment, the reactor was first loaded with an amount of catalyst equivalent with 0.1 mmol active amine sites, 51.7 to 55.0 g DMSO as solvent, 0.5 g to 3 g water added (double deionized, Milli-Q®), and 0.25 g methyl 4-nitrobenzoate ($>99\%$, Sigma-Aldrich) as internal standard. This mixture was then heated to 55 °C, under constant stirring. Acetone (45 g) was separately heated to 55 °C and was used to dissolve 0.45 g 4-nitrobenzaldehyde before injecting in the reactor. Acetone was added in excess, in order to suppress the direct interaction of 4-nitrobenzaldehyde with the amine site. The amount of solvent was adapted according to the amount of water that is added to the reactor in order to avoid effects of a concentration change on the measured kinetics. The temperature in the reactor was maintained at 55 °C using a PID-controller (CAL 9500P), with a thermocouple inside the reactor vessel. This PID controller steered both an electrical heating jacket as well as a cooling unit for an adequate temperature control. The reaction mixture was mechanically stirred at 600 rpm. The time of injection was taken as the start of the reaction ($t = 0$). The reaction was monitored for 4 h by taking a sample (0.3 mL) of the reaction mixture every 15 min during the first hour, and subsequently every 30 min for the remaining 3 h. For each experiment, the total decrease of reaction volume due to sampling was less than 5% whereby the effect of sampling on the kinetic data is considered to be negligible.

After the reaction, the spent catalyst was removed from the reactor, filtered, and stored in a desiccator, in order to avoid atmospheric water vapor from interacting with the catalyst. All recycling experiments were performed by repeating the procedures described above using the recovered spent catalyst within maximum 24 h after the previous run. In order to characterize the surface intermediates on the spent catalysts with Raman spectroscopy and ^{13}C NMR, the catalysts were additionally stirred in 100 mL chloroform ($>99.8\%$, $<50\text{ ppm H}_2\text{O}$, Carl Roth) for 4 h, filtered, and vacuum dried for 24 h.

2.6. Catalytic performance testing in a continuous-flow liquid-phase reactor

Stability tests were performed in a liquid-phase packed-bed tubular reactor, which was developed in-house. A continuously gently stirred liquid feed mixture was fed at the top of the reactor with a HPLC pump (Eldex Laboratories model 2SMP). The reactor tube itself is made of stainless steel 316 with an inner diameter of 80 mm and length of 300 mm. At 100 mm from the bottom, a fine stainless steel mesh is installed to support the catalyst bed. The reactor is electrically heated, with its temperature being controlled at 55 °C by an outer thermocouple with an Omron E5CK PID controller. The temperature in the catalyst bed was measured with an internal thermocouple of 1 mm and allowed confirming the absence of radial temperature gradients. The backpressure is generated in the effluent section using a 1.8 barg check valve. Manometers at the entrance and outlet of the reactor allowed verifying the absence of a significant pressure drop over the reactor. A three-way valve after the backpressure valve allowed to periodically draw samples from the reactor effluent. The reactor was operated in the intrinsic kinetics regime, as has been verified by the proper correlations [48], and is summarized in the Supporting Information.

The feed mixture composition was equivalent to the batch reactor feed composition, consisting of 0.45 wt% 4-nitrobenzaldehyde, 44.6 wt% acetone, 52.5 wt% DMSO, 0.25 wt% methyl 4-nitrobenzoate (internal standard) and 2.19 wt% water. The activity of the cooperative acid-base catalyst and the monofunctional



Scheme 1. Aldol reaction of acetone and 4-nitrobenzaldehyde towards the aldol adduct 4-hydroxy-4-(4-nitrophenyl)butan-2-one, and dehydration to the condensation product 4-(4-nitrophenyl)-3-buten-2-one.

base catalyst were compared using the conversion at the same site time. Site time is defined as the space time $\frac{W}{F_{4-NB}^0}$, multiplied with the active site concentration C_{site} . With W (kg_{cat}) the catalyst mass and F_{4-NB}^0 ($\frac{mol_{4-NB}}{s}$) the molar inlet feed of 4-nitrobenzaldehyde and C_{site} ($\frac{mol_{site}}{kg_{cat}}$) determined with CHNS analysis, site time has units ($\frac{mol_{site}s}{mol_{4-NB}}$).

2.7. Sample analysis, quantification of effluent composition, and defining the catalyst activity

The reaction samples were analyzed using a reversed-phase high-performance liquid chromatograph (RP-HPLC), from Agilent (1100 series) using the same procedure as reported before [29]. The HPLC Eclipse XDB-C18 column was operated at 30 °C using a gradient method with water (0.1% trifluoroacetic acid, Acros) and 30 v% to 62 v% acetonitrile (HPLC grade, Acros) as solvents. This method separates all the components in a period of 14 min. The components were identified using a UV-detector with a variable wavelength that has been programmed for an optimal absorption for each component. Quantification of the different components in the reaction mixture was performed by relating the surface areas of the component peaks to the amount of internal standard added to the reactor. The catalyst activity in the batch reactor was quantified by the turnover frequency, which was determined from the slope of the initial linear part of the conversion of 4-nitrobenzaldehyde as a function of reaction time, the concentration of active amine sites and the initial concentration of 4-nitrobenzaldehyde. The catalytic activity in the continuous-flow reactor was quantified by comparing conversions at the same site time. Repeat experiments have indicated that the experimental error in both reactors, calculated as the 95% confidence interval, was below 5%. With the rule of error propagation, it was determined that ratios of the TOF values in the batch reactor have an experimental error of about 10%.

3. Results and discussion

3.1. Catalyst characterization and validation of the synthesis procedure

The specific BET surface area, average pore size, and total pore volume of the silica gel support and the synthesized catalysts were determined from the nitrogen adsorption–desorption isotherms and are summarized in Table 1. The functionalization of the pristine support material, and further endcapping of the silanol groups with trimethylsilyl groups, caused a small decrease in surface area and pore volume. This decrease can be directly related to a decrease in free volume and an increase in catalyst mass, which is typically observed after the functionalization of these materials [49]. The catalyst, however, retained its mesoporous structure and average pore size of 5 nm after functionalization and endcapping of the silanol groups.

The presence of methylaminopropyl groups on the surface was verified with Diffuse Reflectance Infrared Fourier Transform (DRIFT) spectroscopy, as can be seen in Fig. 1S in Supporting

Table 1

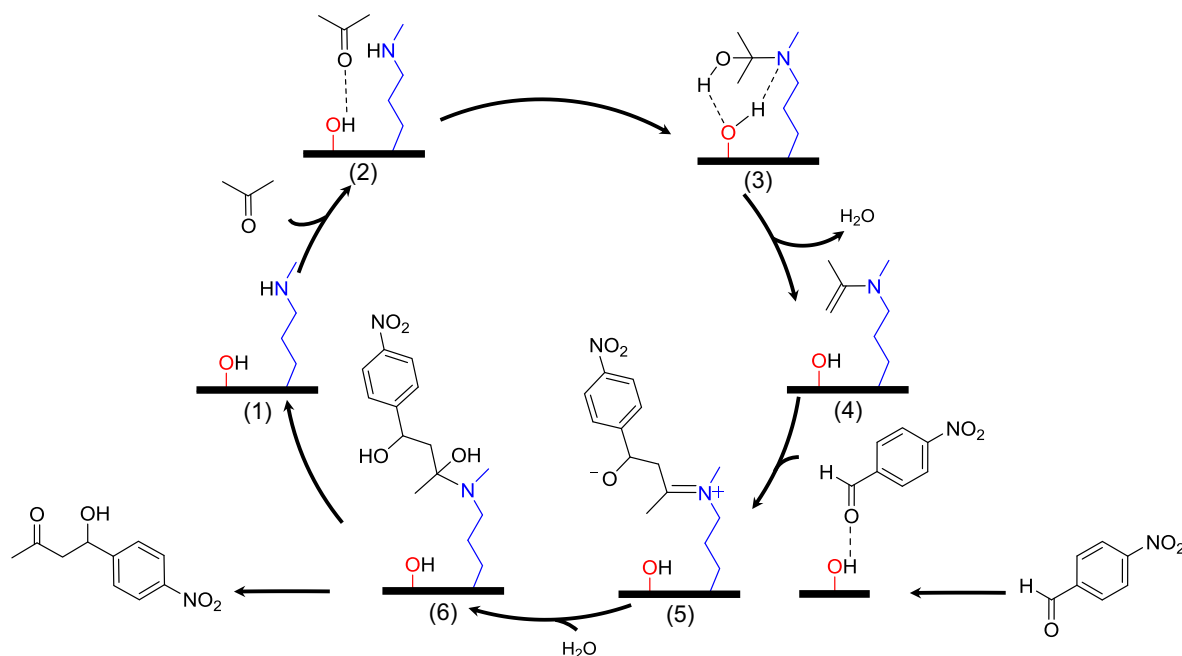
Catalyst properties, for both the cooperative acid-base catalyst as well as the monofunctional base catalyst, fresh and spent in the aldol reaction of acetone with 4-nitrobenzaldehyde. BET surface area, pore size and pore volume are determined via nitrogen adsorption–desorption measurements.

	BET surface area ± 30 (m ² /g)	Pore size ± 0.3 (nm)	Pore volume ± 0.04 (cm ³ /g)
Silica gel 60	451	5.7	0.70
Cooperative acid-base catalyst			
Fresh	314	5.6	0.52
Spent	296	5.6	0.48
Monofunctional base catalyst			
Fresh	272	5.4	0.45
Spent	280	5.2	0.44

Information. In the pristine silica gel support material, a pronounced narrow peak at 3745 cm^{−1} indicated the presence of free silanol groups on the surface. After reaction with N-methylamino propyltrimethoxysilane (MAPTMS), several bands appeared in the region between 2800 cm^{−1} and 3000 cm^{−1}, characteristic of the C–H stretching vibrations of the methylaminopropyl group attached to the surface [29]. At 3305 cm^{−1} a small, broad peak indicates the presence of N–H vibrations. The peak that remains at 3745 cm^{−1} confirms that free silanol groups were still present after grafting. When the catalyst was treated with HMDS to endcap the residual silanol groups, the peak at 3745 cm^{−1} effectively disappeared, as is shown in Fig. 1S. The endcapping of the silanol groups resulted in an increased intensity of the C–H stretching vibrations at 2960 cm^{−1} from the trimethylsilyl groups that replaced the silanol groups. Using CHNS analysis, the amine loading was determined to be 0.17 mmol/g. Using HMDS as a rough silanol titrator, the amount of silanol groups was estimated at 0.69 mmol/g. This indicates that there are at least 4 silanol groups available for each amine site in the cooperative acid-base catalyst, as was targeted during the catalyst synthesis.

3.2. Catalytic performance in the aldol reaction of acetone with 4-nitrobenzaldehyde

The catalytic reaction performed in this work is the enamine catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde towards the primary aldol adduct 4-hydroxy-4-(4-nitrophenyl)butan-2-one, followed by dehydration to the secondary condensation product 4-(4-nitrophenyl)-3-buten-2-one (Scheme 1). The proposed reaction mechanism using a methyl substituted secondary amine promoted by surface silanol groups is given in Scheme 2. The catalytic cycle starts with the formation of a hydrogen bond between the free silanol group (1) and the oxygen of the carbonyl group of acetone (2). Next, the free electron pair of the amine attacks the activated carbonyl group of acetone, and a carbinolamine (3) is formed via a proton-transfer, assisted by the surface silanol group. This carbinolamine dehydrates, yielding an enamine intermediate (4), which then attacks the carbonyl group of an activated 4-nitrobenzaldehyde molecule and forms a new carbon-carbon bond. The formed iminium intermediate (5) is hydrolyzed towards the product carbinolamine (6) and, subsequently, desorbs from the active site as the aldol adduct. When the silanol groups



Scheme 2. Proposed enamine catalytic reaction cycle of the aldol reaction of acetone with 4-nitrobenzaldehyde, catalyzed by a secondary cooperative aminated silica catalyst [22,23,29].

are endcapped with trimethylsilyl groups, the initial activation by hydrogen-bonding, as well as the cooperativity in proton transfer reactions, are absent which results in a lower turnover frequency.

A potential side-reaction for both the cooperative and monofunctional catalyst is the reaction of the amine with the carbonyl group of 4-nitrobenzaldehyde, which yields an iminium ion. This iminium can then react with acetone, via a Mannich type mechanism, and yield the condensate as a primary product [50,51]. However, the direct interaction of 4-nitrobenzaldehyde with the amine is suppressed by using a 260 molar ratio excess of acetone.

Preliminary experiments were performed at 55 °C using 45 g acetone in 55 g DMSO, with 0.1 mmol active amine sites, and 0.45 g 4-nitrobenzaldehyde. DMSO is chosen as solvent because of its full miscibility with water, allowing to investigate the effect of different amounts of water on the catalyst stability and activity. To adequately describe these effects, the initial water content in the organic solvents should also be known. Hence, using coulometric Karl-Fischer titration, the initial water content in the reactor, using stock acetone and DMSO, was determined at 0.19 wt%. Under these conditions, the cooperative acid-base catalyst exhibited a turnover frequency (TOF) of $7.04 \pm 0.40 \cdot 10^{-4} \text{ s}^{-1}$ in the aldol reaction. While, at the same reaction conditions, the monofunctional base catalyst exhibited a lower TOF of $2.56 \pm 0.13 \cdot 10^{-4} \text{ s}^{-1}$, as expected from previous research [29]. The adduct and condensate selectivity amounted to 73% and 27% respectively, for the cooperative acid-base catalyst and 77% and 23% for the monofunctional base catalyst, and remained constant throughout the whole experiment. When reusing the spent catalyst in a second experiment, only 38% of the initial TOF was obtained for the cooperative acid-base catalyst while 77% of the initial TOF was retained for the monofunctional base catalyst.

To obtain insights in the cause of this reduction in initial TOF, characterization of the spent catalysts was performed. The specific BET surface areas, average pore sizes, and total pore volumes of the spent catalysts are also listed in Table 1. The spent catalysts exhibited a slight decrease in surface area and pore volume, but retained their average pore size of 5.0 nm. However, the CHNS elemental analysis indicated a nitrogen content increase of 60% for the spent

cooperative acid-base catalyst and a 15% increase for the spent monofunctional base catalyst. Moreover, as will be discussed in more detail below, the originally white catalyst changed to dark yellow and retained this color even after additional stirring in chloroform and drying. This color change, together with the higher nitrogen content, indicates that the changes in catalytic behavior upon recycling may be caused by surface species that remain on the catalyst.

Raman spectroscopy of these spent catalysts was performed to identify the organic groups in the species remaining on the catalyst surface. The Raman spectrum is displayed in Fig. 1a for the spent cooperative acid-base catalyst, and Fig. 1b for the spent monofunctional base catalyst. The spectra for both catalysts exhibit sharp peaks at 1630 cm^{-1} , 1590 cm^{-1} , 1340 cm^{-1} and 1110 cm^{-1} . These correspond to, respectively, a C=C stretching band conjugated with an aromatic group, an aromatic C=C stretching, a symmetric NO_2 stretch and a weak band due to aromatic in-plane C-H deformation vibrations [52]. The bands below 300 cm^{-1} are characteristic of the lattice vibrations of the Si—O—Si network.

Further characterization of the spent catalyst was performed with ^{13}C cross-polarization/magic-angle-spinning (CP/MAS) NMR spectroscopy. The spectrum is displayed in Fig. 2 for the spent cooperative acid-base catalyst. The peak at 50 ppm can be associated with residual methoxy groups from the amine precursor that did not react with the surface silanol groups. The three peaks at 8, 22 and 49 ppm are associated with the sp^3 carbon atoms of the propyl chain and the peak at 33 ppm is associated with the methyl function of the secondary amine. Additional bands are observed at 147 ppm, originating from an aromatic carbon attached to a nitro group and 127 ppm and 123 ppm from aromatic carbons. The shoulder peak at 150 ppm can be assigned to the aromatic carbon in para-position of the nitro group when bounded to a sp^3 carbon. When bounded to a sp^2 carbon, the corresponding peak appears around 144 ppm and is indistinguishable from the large peak at 147 ppm. The small broad peak at 70 ppm can be assigned to an sp^3 carbon attached to both the aromatic ring and an alcohol function, while the small peak at 38 ppm can be assigned to an sp^3 carbon atom attached to the carbon atom at 70 ppm and an sp^2 carbon atom.

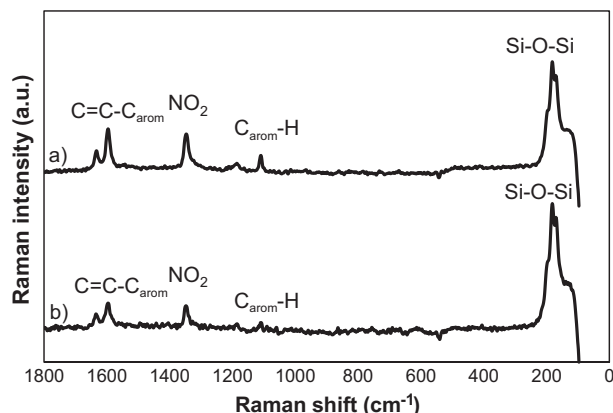
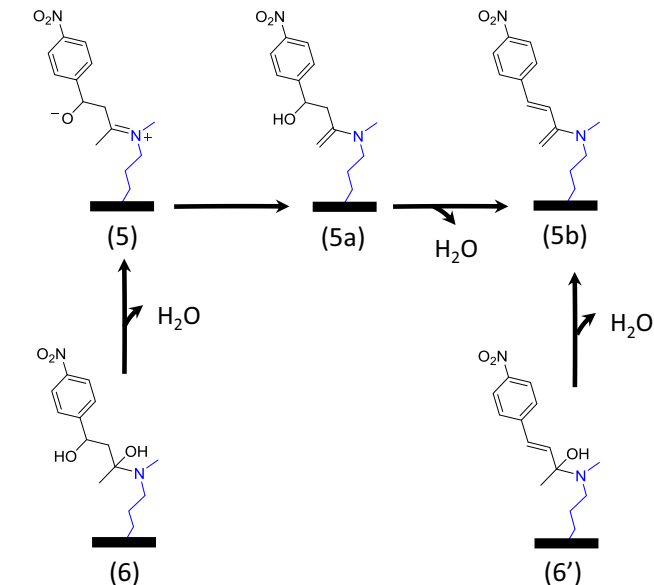


Fig. 1. Raman spectrum of the spent cooperative acid-base catalyst (a) and spent monofunctional base catalyst (b).

The Raman and ^{13}C NMR spectra indicate that the species on the surface of the spent catalysts are derivatives of 4-nitrobenzaldehyde. Due to the absence of peaks in the ^{13}C NMR between 170 ppm and 180 ppm and in the Raman spectrum at 1700 cm^{-1} , corresponding to carbonyl groups from aldehydes or ketones, physisorbed 4-nitrobenzaldehyde, or physisorbed products, can be excluded. The direct addition of 4-nitrobenzaldehyde with the secondary amine did not lead to the observed Raman peaks. This is shown in Fig. 2S (Supporting Information), which is a Raman spectrum of a catalyst that was exposed to 4-nitrobenzaldehyde in DMSO, without acetone, under reaction conditions.

Several possible surface species, stemming from the iminium intermediate (5 in Scheme 2), are proposed in Scheme 3. This iminium intermediate is formed after the attack of the enamine on the carbonyl group of 4-nitrobenzaldehyde, or from the aldol adduct readsorption (6) and subsequent dehydration. It can subsequently rearrange towards the enamine form (5a). Upon dehydration of (5a), the enamine form of the condensation product (5b) is formed. This latter species can also be formed from the dehydration of the carbinolamine (6'). It can, however, reasonably be expected that the pathway via product readsorption on a free amine site only occurs to a limited extent due to the large excess of acetone used.



Scheme 3. Possible species on the surface of a spent catalyst corresponding with the characterization results and their proposed formation pathways. The iminium intermediate species (5) from the catalytic cycle in Scheme 2, or from the aldol adduct readsorption via (6), can further dehydrate into a conjugated species (5b) via its enamine intermediate (5a). Condensate readsorption via (6') also yields the conjugated species (5b).

Because charged species are unlikely to exist on a dried catalyst, the iminium intermediate is expected to only be stable under liquid-phase conditions. Any iminium intermediates that are on the surface of the catalyst after removal of the material from the reactor by filtration, are expected to convert to (5a), or directly dehydrate to (5b). The 4 different candidate species to be present on the surface of a spent catalyst correlating with the Raman spectroscopy and ^{13}C NMR characterization results, are (5a), (5b), (6) and (6') in Scheme 3. Recent computational research on the relative stability of enamines [53] has shown that conjugated enamines, such as dienamines with phenyl groups, are thermodynamically stable due to their conjugation effects. Possibly, the enamine species (5b) thus blocks access to the catalytic site when recycling the catalyst in a subsequent experiment.

Water was co-fed in the reactor to enhance the hydrolysis of the iminium intermediate (5) in the catalytic cycle and, hence, prevent the formation of the site blocking species as indicated in Scheme 3. In this work, the polar solvent DMSO was chosen because of its complete miscibility with water in a broad range of conditions. Even though this solvent does not yield the highest turnover frequencies (TOF) for amine catalyzed aldol reactions, it allows to perform a mechanistic investigation of the deactivation phenomena and the effect of co-feeding water.

3.3. Effect of water on the reusability of aminated silica catalysts for aldol reactions in the batch reactor

Several catalytic experiments were performed with a varying amount of water added to the starting mixture of the batch reactor. Care was taken that the amount of solvent, i.e., DMSO, was adapted to compensate for the volume of the water added to the system. Experiments were also performed with dried acetone, resulting in a total water content of 0.09 wt% in the reactor. After 4 h of reaction, the spent catalysts were removed from the reactor, dried, and reused in a second experiment under identical operating conditions, or stored in a desiccator for further characterization.

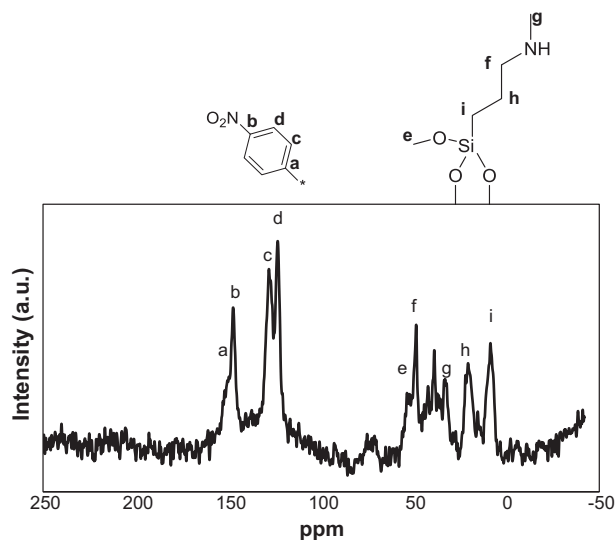


Fig. 2. ^{13}C CP/MAS NMR spectrum of the spent cooperative acid-base catalyst. The grafted secondary amine can be identified in the spectrum, as well as the carbon atoms originating from the aromatic ring with a nitro substituent.

The effect of water on the activity of the cooperative acid-base and the monofunctional base catalysts, as indicated by the TOF, is displayed in Fig. 3a and b respectively. When 0.69 wt% water was present in the reactor with the cooperative acid-base catalyst, the TOF of the first run amounted to $9.38 \pm 0.47 \cdot 10^{-4} \text{ s}^{-1}$, compared to $7.04 \pm 0.35 \cdot 10^{-4} \text{ s}^{-1}$ without water addition. For the monofunctional base catalyst, an increase from $2.56 \pm 0.13 \cdot 10^{-4} \text{ s}^{-1}$ to $3.66 \pm 0.18 \cdot 10^{-4} \text{ s}^{-1}$ is observed. Such an enhancement in the reaction rate has also previously been observed when a small amount of water is co-fed when using homogeneous amino-acid catalysts [54]. This can be related to the increased hydration of the reactive iminium species on the catalytic surface, which leads to an increased product desorption rate. When the water amount was further increased up to 3.19 wt%, the TOF lowered again to $7.06 \pm 0.35 \cdot 10^{-4} \text{ s}^{-1}$ for the cooperative acid-base catalyst. This can be attributed to (i) an unfavorable shift in the carbinolamine-enamine equilibrium [46,50], (ii) protonation of amine groups and (iii) hydrogen bonding of amine sites with surface silanol groups, assisted by water molecules [55]. The decrease in TOF with 3.19 wt% water also occurs for the monofunctional base catalyst, albeit to a lesser extent. This indicates that endcapping the silanol groups, and thereby increasing the hydrophobicity of the support, decreases its susceptibility to the negative effects of water.

During a single experiment, the selectivity rapidly converged to a constant value. Additionally, when more water was included in the starting mixture in the reactor, a pronounced shift in selectivity towards the aldol adduct was observed for both catalysts (Fig. 3S in Supporting Information). Hence, it can be concluded that the aldol adduct and condensate are in equilibrium at the investigated conditions, and the addition of water shifts this equilibrium to the side of the aldol adduct.

The catalyst reusability ratios are calculated as the ratio of TOF in the second run to that in the first run and are also displayed in Fig. 3. The reusability of the cooperative acid-base catalyst increased from 28% with 0.09 wt% water to a maximum of 70% with 0.69 wt% water. Correspondingly, the reusability of the monofunctional base catalyst increased from 58% with 0.09 wt% water to 92% with 0.69 wt% water, and remained constant for higher water amounts. The presence of silanol groups in the cooperative acid-base catalyst therefore seems to limit the reusability that can be achieved. Yet, almost full reusability of the monofunctional base catalyst can be achieved with at least 0.69 wt% water. This demonstrates how deactivation of the amine active sites can be minimized by the addition of water. The catalyst characterization data in Tables 1S and 2S (Supporting Information) shows that, at the time scale of these batch experiments,

structural degradation of the porous silica network is not a pronounced deactivation phenomenon for both types of catalyst.

It should further be noted that when a spent monofunctional base catalyst, after use under dry reaction conditions, was recycled for a second experiment with 2.19 wt%, only 70% reusability was achieved. This shows that, while such an amount of water can prevent the deactivation of the amine active site by favoring the hydrolysis of the iminium intermediate during the first run, it cannot fully regenerate the already deactivated sites after a first run in which insufficient water was used.

Raman spectra were also recorded for each spent catalyst, and are plotted as a function of the water amount in the reactor in Fig. 4. It can be seen that the peaks at 1630 cm^{-1} , 1600 cm^{-1} , 1340 cm^{-1} and 1110 cm^{-1} , associated with the aromatic species bearing a nitro group, gradually disappear when more water is present in the reactor.

Additionally, a ^{13}C NMR spectrum was recorded for a cooperative acid-base catalyst that was spent in a reaction with 1.19 wt% water in the reactor and is displayed in Fig. 5. Also here, the characteristic peaks of the nitro-containing aromatic species decreased considerably due to the addition of water.

As mentioned above, a distinct change in color of the spent catalyst was observed after reaction, which persisted after stirring the catalyst in chloroform. By co-feeding water, it appears that the colorization of the spent catalyst becomes less pronounced as a function of the amount of water, as is shown in Fig. 6. Removing inherently present water from the stock acetone solution by drying caused the cooperative acid-base catalyst to appear dark red after being spent. The color variations of the spent monofunctional base catalyst seem to be shifted slightly towards the colors of the cooperative acid-base catalysts spent after having used a higher amount of water. Hence, the same trends are expected for the monofunctional base catalysts.

UV–Vis reflection characterization of the spent cooperative acid-base catalysts was performed and is displayed in Fig. 7. When more water was added to the reactor, the peak intensity of the spent catalyst is decreased. This indicates that less chromophoric surface species are present on a spent catalyst when more water is added to the reactor.

The peak maximum for the catalysts spent with 0.09 wt% of water is at 520 nm, while the peak maximum for the catalysts spent with at least 1.19 wt% of water is located at 432 nm. This shift to shorter wavelengths is a typical phenomenon that can be seen when the degree of conjugation in an organic compound decreases. Since this shift correlates with the increased reusability,

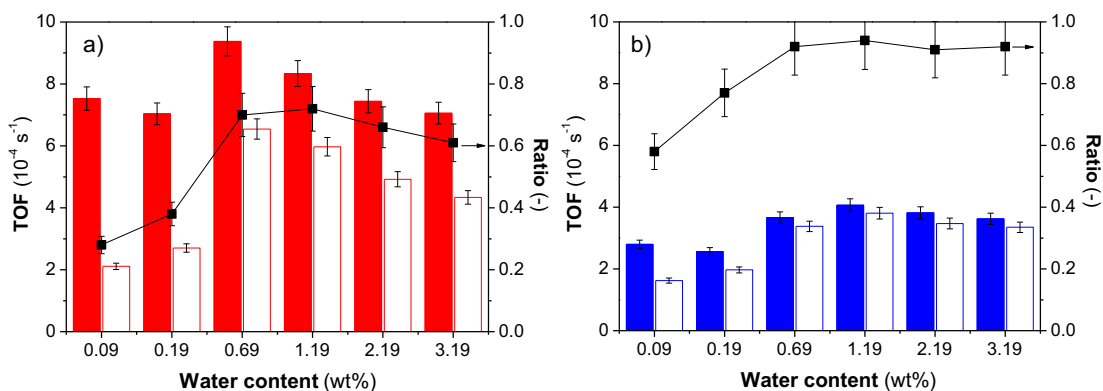


Fig. 3. Turnover frequency (TOF – s^{-1}) for the aldol reaction of acetone with 4-nitrobenzaldehyde, using a cooperative acid-base catalyst (a, red) and a monofunctional base catalyst (b, blue) as a function of the amount of water in the reactor. Full bars represent the first run, empty bars the second run, and the right axis indicates the ratio between the TOF observed in the second and the first run. Lines are a guide for the eye. Absolute water content in the reactor has been determined with Karl-Fischer titrations. Error bars indicate a 95% confidence interval. ($T = 55^\circ\text{C}$, 0.45 g 4-nitrobenzaldehyde, 45 g acetone, 52–55 g DMSO, 0.20 g methyl 4-nitrobenzoate, 0.5 g to 3.0 g water added, 0.31 wt% water in stock acetone, 0.09 wt% water in dried acetone, 0.09 wt% water in stock DMSO).

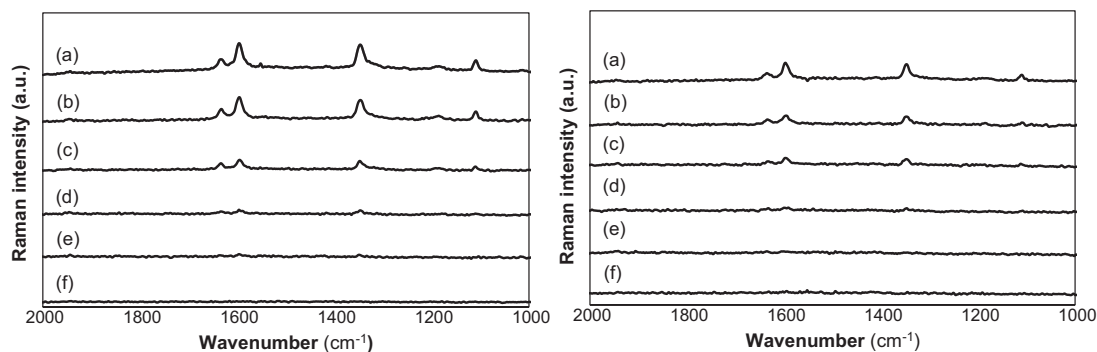


Fig. 4. Raman spectrum of the spent cooperative acid-base catalyst (left) and the spent monofunctional base catalyst (right) (a: 0.09 wt% water, b: 0.19 wt% water, c: 0.69 wt% water, d: 1.19 wt% water, e: 2.19 wt% water and f: 3.19 wt% water).

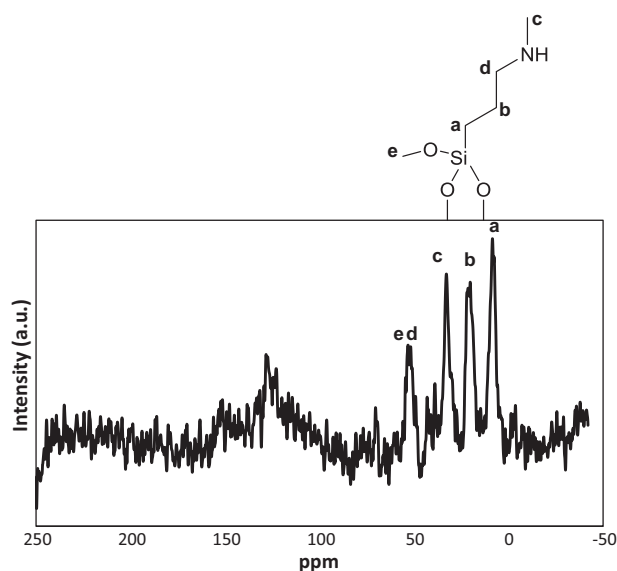


Fig. 5. ^{13}C NMR result of a cooperative acid-base catalyst, spent in the aldol reaction of 4-nitrobenzaldehyde with acetone, using 1.19 wt% water in the reactor.

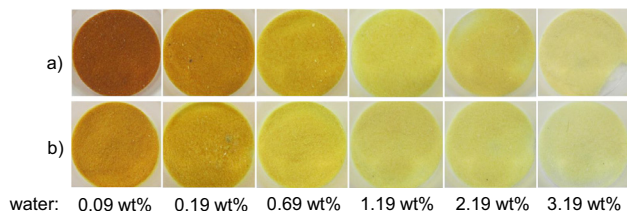


Fig. 6. Spent catalyst color as a function of the water amount in the reactor. (a) Cooperative acid-base, (b) monofunctional base catalyst.

a more highly conjugated species such as 5b (Scheme 3) is believed to be responsible for the deactivation of the catalyst. The possible chromophoric species at 432 nm, present on the spent catalysts after use with at least 1.19 wt% water, could then correspond to the more hydrated species 5a, 6 and 6' (Scheme 3).

As mentioned above, the nitrogen content on the spent catalyst was higher than that on the fresh catalyst. Hence, the catalysts spent using different amounts of water in the reactor were subject to CHNS elemental analysis. The observed amount of nitrogen on the spent catalyst as a function of the amount of water used in the experiment is expressed relative to the total amount of active sites on a fresh catalyst, and is defined as 'excess N' in Fig. 4S in

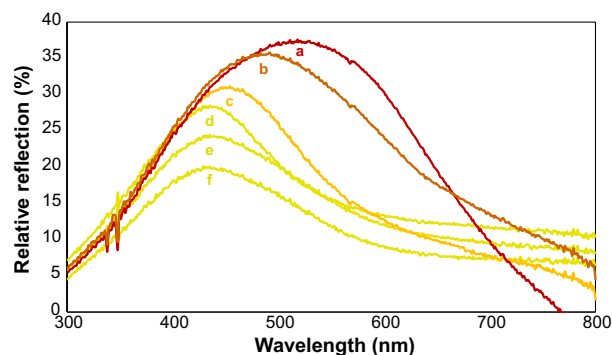


Fig. 7. Percentage UV-Vis reflection as a function of wavelength of the spent cooperative acid-base catalysts, relative to a fresh catalyst (a: 0.09 wt% water, b: 0.19 wt% water, c: 0.69 wt% water, d: 1.19 wt% water, e: 2.19 wt% water and f: 3.19 wt% water).

Supporting Information. Since possible leaching effects are masked by the increase in nitrogen content, it has also been verified that there was no active site leaching by performing batch experiments with 4-chlorobenzaldehyde as a substrate, and ethyl-4-methylbenzoate as internal standard, under the same reaction conditions. These results are also included in the Supporting Information, Fig. 4S, and prove that leaching is not a significant deactivation factor at the investigated batch reactor conditions. The increase in the nitrogen content of the spent catalyst compared to the fresh catalyst can be used to quantify the fraction of sites that are covered with a nitrogen containing species, such as the ones proposed in Scheme 3. From the results in Fig. 4S it is clear that, when using 0.09 wt% water, also denoted as 'dry' conditions, the fraction of covered sites is significantly larger (90%) on the spent cooperative acid-base catalyst than on the spent monofunctional base catalyst (40%). This could be the result of the relatively low amount of water with respect to active sites under these 'dry' conditions, i.e., with 0.09 wt% of water, only 5 mmol of water is available for 0.1 mmol amines and 0.4 mmol silanol groups. Hence, adsorption of several water molecules on the hydrophilic silanol groups can already significantly lower the amount of water molecules available for iminium ion hydrolysis. When no silanol groups are present for water adsorption, as is the case in the monofunctional base catalyst, more water is available for iminium ion hydrolysis. When a water excess is present, i.e. 0.69 wt% or more, this discrepancy between both catalysts disappears.

It can be concluded from the Raman spectra, the UV-Vis reflection spectra, the elemental CHNS analysis and the ^{13}C NMR, that water reduces the amount of surface species that remain on a spent catalyst and increases the catalyst's reusability. It however appears that, despite having no remaining surface species on the

amine site, the activity of the cooperative acid-base catalyst can only be regained for 70% by adding water.

3.4. Differences in activity and stability of the cooperative acid-base and the monofunctional base catalysts

It was shown in the previous section that sufficient water is required to minimize the deactivation of the amine sites. Yet, only a maximum reusability of 70% can be achieved for the cooperative acid-base catalyst, while the monofunctional base catalyst is almost entirely reusable. Additionally, it is seen that adding more water even seems to decrease the reusability of the cooperative acid-base catalyst. To investigate the behavior of the cooperative acid-base catalyst with high water contents, and to confirm the stability of the monofunctional base catalyst without having to remove and recycle the catalyst in numerous consecutive batch experiments, continuous-flow experimentation was performed under the same reaction conditions. Water is added to the feed amounting to 2.19 wt%. This large amount has been selected to reduce the deactivation of the amine sites to a minimum by complete iminium ion hydrolysis, and to understand the potential negative effects of a large amount of water on the catalyst stability. Both catalysts were compared at the same site time of $165.1 \text{ mol}_{\text{site}}^{-1} \text{ s mol}_{4\text{-nitrobenzaldehyde}}^{-1}$, which indicates that the average time available, per site, for a molecule to react is identical. Fig. 8 shows the conversion for both catalysts with time-on-stream.

Till 7 h on stream, the cooperative acid-base catalyst exhibited a higher activity than the monofunctional base catalyst. This agrees well with the observations made in the batch reactor, where the cooperative acid-base catalyst exhibited a higher activity than the monofunctional base catalyst at the same conditions. However, after 7 h on-stream, the activity of the cooperative catalyst has dropped to the same level as the monofunctional base catalyst, which has only slightly deactivated after such a time on stream. This first, and most rapid, deactivation of the cooperative acid-base catalyst is attributed to the loss of the cooperativity between the silanol groups and the amine active sites. Indeed, when the cooperative ability has been completely lost after 7 h on stream, only the activity of the isolated amine site remains, whereby the activity of the cooperative acid-base catalyst has been reduced to that of the monofunctional base catalyst. The silanol groups, that are responsible for the cooperative effect, seem to lose their hydrogen-bonding ability towards the carbonyl substrates. This could be due to water deprotonating the silanol groups, or forming an extensive multilayer coverage on the surface of the silica gel [56], which limits access to the silanol groups for the carbonyl

substrates. Dehydration of the silica support material, and complete regeneration of the silanol group's cooperative ability, is only possible at elevated temperatures which would destroy the organic moieties on our catalyst. This silanol group deactivation also explains why these cooperative acid-base catalysts are not reusable in the batch reactor, and the addition of larger amounts of water seems to even decrease the reusability ratio, even though the amine site itself can be made fully reusable.

After 8 h on-stream, the slope of the evolution of the conversion with time-on-stream for the cooperative acid-base catalyst changes. The deactivation occurs at a reduced rate, yet, it remains faster than the decrease in conversion with the time-on-stream exhibited by the monofunctional base catalyst. In this regime of prolonged exposure to the aqueous feed, the deactivation is most likely caused by hydrolysis reactions of the silica material that cause aminosilane leaching, structural degradation of the support material and silica dissolution. This is suggested by the drop in surface area and pore volume for the cooperative acid-base catalyst, as is indicated in Table 3S (Supporting Information). The slower deactivation rate of the monofunctional base catalyst, and the more stable surface area and pore volume after catalysis, could then be the result of the end-capping of the silanol groups with trimethylsilyl groups, which introduced a more hydrophobic surface environment. This increased support stability by trimethylsilylation has already been observed for other mesoporous silica materials such as MCM-48 [57]. It should, however, be noted that endcapping with HMDS is never complete due to steric hinderance, and that water can still interact with the silica surface under the umbrellas of the trimethylsilyl groups [58], causing hydrolysis and subsequent deactivation with long time-on-stream. Hence, the monofunctional base catalyst is not unconditionally stable. A more stable catalyst could be developed in the form of a periodic mesoporous organosilica material with hydrophobic organic groups in the support material [35].

4. Conclusions

For the first time, the reusability of aminated mesoporous amorphous silica catalysts was thoroughly investigated for the aldol reaction of 4-nitrobenzaldehyde with acetone in DMSO. It is found that, under 'dry' reaction conditions, both the cooperative acid-base catalyst, as well as the monofunctional base catalyst, exhibit a significantly poorer performance in consecutive batch experiments. Spent catalyst characterization using Raman spectroscopy, ^{13}C NMR, and UV–Vis characterization, allowed identifying site blocking species originating from the iminium intermediate in the catalytic cycle. To increase the hydration rate of this iminium intermediate and, hence, reduce their conversion into site blocking species, water should be co-fed to the batch reactor. This results in an increased reusability up to 70% for the cooperative acid-base catalyst and an almost complete reusability for the monofunctional base catalyst.

Using continuous-flow experimentation at operating conditions where the formation of site blocking species is minimized, the difference in deactivation behavior between the cooperative and monofunctional catalyst has been assessed further. In the first instance, a relatively rapid loss of the cooperative ability of the catalyst is observed, most likely due to the local buildup of water, or the deprotonation of the silanol groups by water. With a longer time-on-stream, the activity of both catalysts further decreases more moderately, which can be related to hydrolysis reactions of the silica network that lead to aminosilane leaching, support degradation, and silica dissolution. This deactivation being even less pronounced for the monofunctional base catalyst than for the cooperative one, is attributed to its more pronounced hydrophobicity owing to the trimethylsilyl groups used for endcapping.

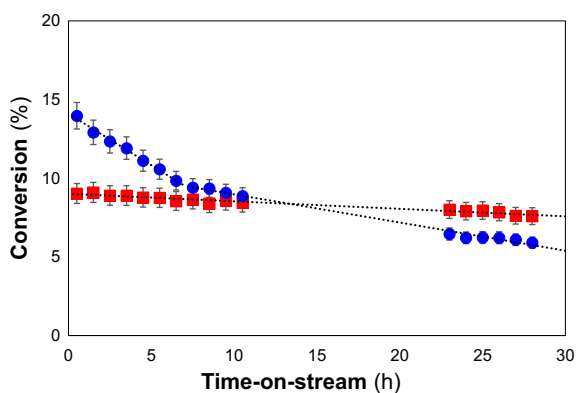


Fig. 8. Stability of the cooperative acid-base catalyst (●, blue) and the monofunctional base catalyst (■, red) with time-on-stream for 28 h. ($T = 55^\circ\text{C}$, $P_{\text{tot}} = 1.8 \text{ bar}$, site time = $165.1 \text{ mol}_{\text{site}}^{-1} \text{ s mol}_{4\text{-nitrobenzaldehyde}}^{-1}$, 0.45 wt% 4-nitrobenzaldehyde, 44.6 wt% acetone, 52.5 wt% DMSO, 0.25 wt% methyl 4-nitrobenzoate, 2.19 wt% water). Lines are a guide to the eye.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jcat.2018.02.016>.

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